The mechanism by which ZDV reduced transmission in PACTG 076 has not been fully defined. The effect of ZDV on maternal HIV-1 RNA does not fully account for the observed efficacy of ZDV in reducing transmission. Preexposure prophylaxis of the fetus or infant may be a substantial component of protection. If so, transplacental passage of antiretroviral drugs would be crucial for prevention of transmission. Additionally, in placental perfusion studies, ZDV has been metabolized into the active triphosphate within the placenta *[51, 52]*, which could provide additional protection against *in utero* transmission. This phenomenon may be unique to ZDV, because metabolism to the active triphosphate form within the placenta has not been observed in the other nucleoside analogues that have been evaluated (i.e., ddI and ddC) *[53, 54]*.

In PACTG 076, similar rates of congenital abnormalities occurred in infants with and without *in utero* ZDV exposure. Data from the Antiretroviral Pregnancy Registry also have demonstrated no increased risk for congenital abnormalities among infants born to women who receive ZDV antenatally compared with the general population *[55]*. Data for uninfected infants from PACTG 076 followed from birth to a median age of 4.2 years (range 3.2–5.6 years) have not indicated any differences in growth, neurodevelopment, or immunologic status among infants born to mothers who received ZDV compared with those born to mothers who received placebo *[56]*. No malignancies have been observed in short-term (i.e., up to six years of age) follow-up of more than 727 infants from PACTG 076 and from a prospective cohort study involving infants with *in utero* ZDV exposure *[57]*. However, follow-up is too limited to provide a definitive assessment of carcinogenic risk with human exposure. Long-term follow-up continues to be recommended for all infants who have received *in utero* ZDV exposure (or *in utero* exposure to any of the antiretroviral drugs).

The efficacy of ZDV chemoprophylaxis for reducing HIV transmission among populations of infected women with characteristics unlike those of the PACTG 076 population has been evaluated in another perinatal protocol (i.e., PACTG 185) and in prospective cohort studies. PACTG 185 enrolled pregnant women with advanced HIV-1 disease and low $CD4^+$ T-lymphocyte counts who were receiving antiretroviral therapy; 24% had received ZDV before the current pregnancy *[58]*. All women and infants received the three-part ZDV regimen combined with either infusions of hyperimmune HIV-1 immunoglobulin (HIVIG) containing high levels of antibodies to HIV-1 or standard intravenous immunoglobulin (IVIG) without HIV-1 antibodies. Because advanced maternal HIV disease has been associated with increased risk for perinatal transmission, the transmission rate in the control group was hypothesized to be 11%–15% despite the administration of ZDV. At the first interim analysis, the combined group transmission rate was only 4.8% and did not substantially differ by whether the women received HIVIG or IVIG or by duration of ZDV use *[58]*. The results of this trial confirm the efficacy of ZDV observed in PACTG 076 and extend this efficacy to women with advanced disease, low $CD4^+$ count, and prior ZDV therapy. Rates of perinatal transmission have been documented to be as low as 3%–4% among women with HIV-1 infection who receive all three components of the ZDV regimen, including women with advanced HIV-1 disease *[6, 58]*.

Data suggest that antenatal use of combination antiretroviral regimens may further reduce transmission. An open-label, non-randomized study in 445 women with HIV infection in France evaluated adding 3TC at 32 weeks gestation to standard ZDV prophylaxis; 3TC was also given to the infant for 6 weeks in addition to ZDV *[25]*. The transmission rate in the ZDV/3TC group was 1.6% (95% confidence interval, 0.7–3.3%); in comparison, the transmission rate in an historical control group of women receiving only ZDV was 6.8% (95% confidence interval 5.1–8.7%). In a longitudinal epidemiologic study conducted in the U.S. since 1990, transmission was observed in 20% of women with HIV infection who received no antiretroviral treatment during pregnancy; 10.4% who received ZDV alone; 3.8% who received combination therapy without protease inhibitors; and 1.2% who received combination therapy with protease inhibitors *[59]*.

International Antiretroviral Prophylaxis Clinical Trials

In a short-course antenatal/intrapartum ZDV perinatal transmission prophylaxis trial in non-breastfeeding women in Thailand, administration of ZDV 300 mg twice daily for four weeks antenatally and 300 mg every three hours orally during labor was shown to reduce perinatal transmission by approximately 50% compared to placebo *[60]*. Transmission decreased from 19% in the placebo group to 9% in the ZDV group. A second, four-arm factorial design trial in Thailand is comparing administration of ZDV antenatally starting at 28 or 36 weeks gestation, orally intrapartum, and to the neonate for three days or six weeks. At an interim analysis, the transmission rate

was 10% in the arm receiving ZDV antenatally starting at 36 weeks and postnatally for three days to the infant, which was significantly higher than for the long-long arm (antenatal starting at 28 weeks and infant administration for six weeks) *[61]*. The transmission rate in the short-short arm of this study was similar to the 9% observed with short antenatal/intrapartum ZDV in the first Thai study.

A third trial in Africa (PETRA trial) in breastfeeding HIV-infected women has shown that a combination regimen of ZDV and 3TC administered starting at 36 weeks gestation, orally intrapartum, and for one week postpartum to the woman and infant reduced transmission by approximately 50% compared to placebo at age six weeks *[62]*. Transmission at age six weeks was decreased from 15% in the placebo group to 6% with the three-part ZDV/3TC regimen. This efficacy is similar to the efficacy observed in the Thailand study of antepartum/intrapartum short-course ZDV in non-breastfeeding women *[60]*.

Studies have identified two possible intrapartum/postpartum regimens (either ZDV/3TC or nevirapine) that could provide an effective intrapartum/postpartum intervention for those women in whom the diagnosis of HIV is not made until very near to or during labor. The PETRA African ZDV/3TC trial in breastfeeding HIV-infected women also demonstrated that an intrapartum/postpartum regimen, started during labor and continued for one week postpartum in the woman and infant, reduced transmission at age six weeks from 15% in the placebo group to 9% with the two-part ZDV/3TC regimen, a reduction of 40% *[62]*. In this trial, oral ZDV/3TC administered solely during the intrapartum period was not effective in lowering transmission. Another study in Uganda (HIVNET 012), again in a breastfeeding population, demonstrated that a single 200 mg oral dose of nevirapine given to the mother at onset of labor combined with a single 2 mg/kg oral dose given to her infant at 48–72 hours of age reduced transmission by nearly 50% compared to a very short regimen of ZDV given orally during labor and to the infant for one week *[63]*. Transmission at age six weeks was 12% in the nevirapine compared to 21% in the ZDV group. A subsequent trial in South Africa demonstrated similar transmission rates with a modified HIVNET 012 nevirapine regimen (nevirapine given to the woman as a single dose in labor with a second dose at 48 hours postpartum, and a single dose to the infant at age 48 hours) compared to the PETRA regimen of oral ZDV/3TC during labor and for one week after delivery in the mother and infant *[64]*. Transmission rates at 8 weeks of age were 13.3% in the nevirapine arm and 10.9% in the ZDV/3TC arm.

Two clinical trials have suggested that the addition of the HIVNET 012 single dose nevirapine regimen to short-course ZDV may provide increased efficacy in reducing perinatal transmission. A study in non-breastfeeding women in Thailand compared a short-course ZDV regimen (starting at 28 weeks gestation, given orally intrapartum, and for 1 week to the infant) to two combination regimens: short-course ZDV plus single-dose intrapartum/neonatal nevirapine and short-course ZDV plus intrapartum maternal nevirapine only. The short-course ZDV-only arm had enrollment stopped by the Data and Safety Monitoring Board at the first interim analysis because transmission was significantly higher in those receiving ZDV alone group compared to those receiving the intrapartum/neonatal nevirapine combination regimen *[65]*. The study is continuing to enroll to allow comparison of the two combination arms. A second open-label study in Cote d'Ivoire reported a 7.1% transmission rate at age 4 weeks with administration of short-course ZDV (starting at 36 weeks, given orally intrapartum, and for 1 week to the infant) combined with single-dose intrapartum/neonatal nevirapine, which was lower than a non-concurrent historical control group receiving ZDV alone *[66]*.

In contrast to these studies, which evaluated combining single-dose nevirapine with short-course ZDV, a study in the U.S., Europe, Brazil and the Bahamas (PACTG 316) evaluated whether the addition of the HIVNET 012 single-dose nevirapine regimen to standard antiretroviral therapy (at minimum the 3-part full ZDV regimen) would provide additional benefits in lowering transmission. In this study, 1,506 pregnant women with HIV infection who were receiving antiretroviral therapy (77% were receiving combination antiretroviral regimens) were randomized to receive a single dose of nevirapine or nevirapine placebo at onset of labor, and their infants received a single dose (according to the maternal randomization) at age 48 hours. Transmission was not significantly different between groups, occurring in 1.6% of women in the placebo group and 1.4% among women in the nevirapine group *[67]*.

There are some data to suggest post-exposure antiretroviral prophylaxis of infants whose mothers did not receive antepartum or intrapartum antiretroviral drugs may provide some protection against transmission. Although some epidemiological data do not support efficacy of postnatal ZDV alone, other data indicate that there may be some efficacy if drug is started rapidly following birth *[6, 68, 69]*. In a study from North Carolina, the rate of infection in HIV-exposed infants who received only postpartum ZDV

chemoprophylaxis was similar to that observed in infants who received no ZDV chemoprophylaxis *[6]*. However, another epidemiological study from New York State, found that administration of ZDV to the neonate for six weeks was associated with a significant reduction in transmission if the drug was initiated within 24 hours of birth (the majority of infants started within 12 hours) *[68, 69]*. Consistent with a possible preventive effect of rapid postexposure prophylaxis, a retrospective case-control study of health care workers from the United States, France, and the United Kingdom who had nosocomial exposure to HIV-1-infected blood, found that postexposure use of ZDV was associated with reduced odds of contracting HIV-1 (adjusted odds ratio 0.2; 95% CI = 0.1–0.6) *[70]*. Several clinical trials to assess what might be the optimal post-exposure antiretroviral prophylaxis regimen for infants are ongoing.

Perinatal HIV-1 Transmission and Maternal HIV-1 RNA Copy Number

The correlation of HIV-1 RNA levels with risk for disease progression in nonpregnant infected adults suggests that HIV-1 RNA should be monitored during pregnancy at least as often as recommended for persons who are not pregnant (e.g., every three to four months or approximately once each trimester). In addition, HIV-1 RNA levels should be evaluated at 34–36 weeks of gestation to allow discussion of options for mode of delivery based on HIV-1 RNA results and clinical circumstances. Although no data indicate that pregnancy accelerates HIV-1 disease progression, longitudinal measurements of HIV-1 RNA levels during and after pregnancy have been evaluated in only a few prospective cohort studies. In one cohort of 198 HIV-1 infected women, plasma HIV-1 RNA levels were higher at six months postpartum than during antepartum in many women; this increase was observed in women regardless of ZDV use during and after pregnancy *[71]*.

Initial data regarding the correlation of viral load with risk for perinatal transmission were conflicting, with some studies suggesting an absolute correlation between HIV-1 RNA copy number and risk of transmission *[72]*. However, although higher HIV-1 RNA levels have been observed among women who transmitted HIV-1 to their infants, overlap in HIV-1 RNA copy number has been observed in women who transmitted and those who did not transmit the virus. Transmission has been observed across the entire range of HIV-1 RNA levels (including in women with HIV-1 RNA copy number below the limit of detection of the assay), and the predictive value of RNA copy number for transmission in an individual woman has been relatively poor *[71, 73, 74]*. In PACTG 076, antenatal maternal HIV-1 RNA copy number was associated with HIV-1 transmission in women receiving placebo. In women receiving ZDV, the relationship was markedly attenuated and no longer statistically significant *[50]*. An HIV-1 RNA threshold below which there was no risk for transmission was not identified; ZDV was effective in reducing transmission regardless of maternal HIV-1 RNA copy number *[50, 75]*.

More recent data from larger numbers of ZDV-treated infected pregnant women indicate that HIV-1 RNA levels correlate with risk of transmission even among antiretroviral treated women *[60, 76-78]*. Although the risk of perinatal transmission in women with HIV-1 RNA below the level of assay quantitation appears to be extremely low, transmission from mother to infant has been reported in women with all levels of maternal HIV-1 RNA. Additionally, while HIV-1 RNA may be an important risk factor for transmission, other factors also appear to play a role *[78-80]*.

While there is a general correlation between plasma and genital tract viral load, discordance has also been reported, particularly between HIV proviral load in blood and genital secretions *[81-84]*. If exposure to HIV in the maternal genital tract during delivery is a risk factor for perinatal transmission, then plasma HIV-1 RNA levels may not always be an accurate indicator of risk. Long-term changes in one compartment (e.g., such as may occur with antiretroviral treatment) may or may not be associated with comparable changes in other select body compartments. Further studies are needed to better define the effect of antiretroviral drugs on genital tract viral load and the association of such effects on the risk of perinatal HIV transmission. In the short-course ZDV Thailand trial, plasma and cervicovaginal HIV-1 RNA levels were reduced by ZDV treatment and each independently correlated with perinatal transmission *[85]*. The use of the full ZDV chemoprophylaxis regimen, including intravenous ZDV during delivery and the administration of ZDV to the infant for the first six weeks of life, alone or in combination with other antiretrovirals, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level.

Recent epidemiological and clinical trial data suggest that women receiving highly active antiretroviral regimens that effectively reduce HIV-1 RNA to <1,000 copies/mL or undetectable levels have very low rates of perinatal transmission *[25, 59, 67, 86]*. However,